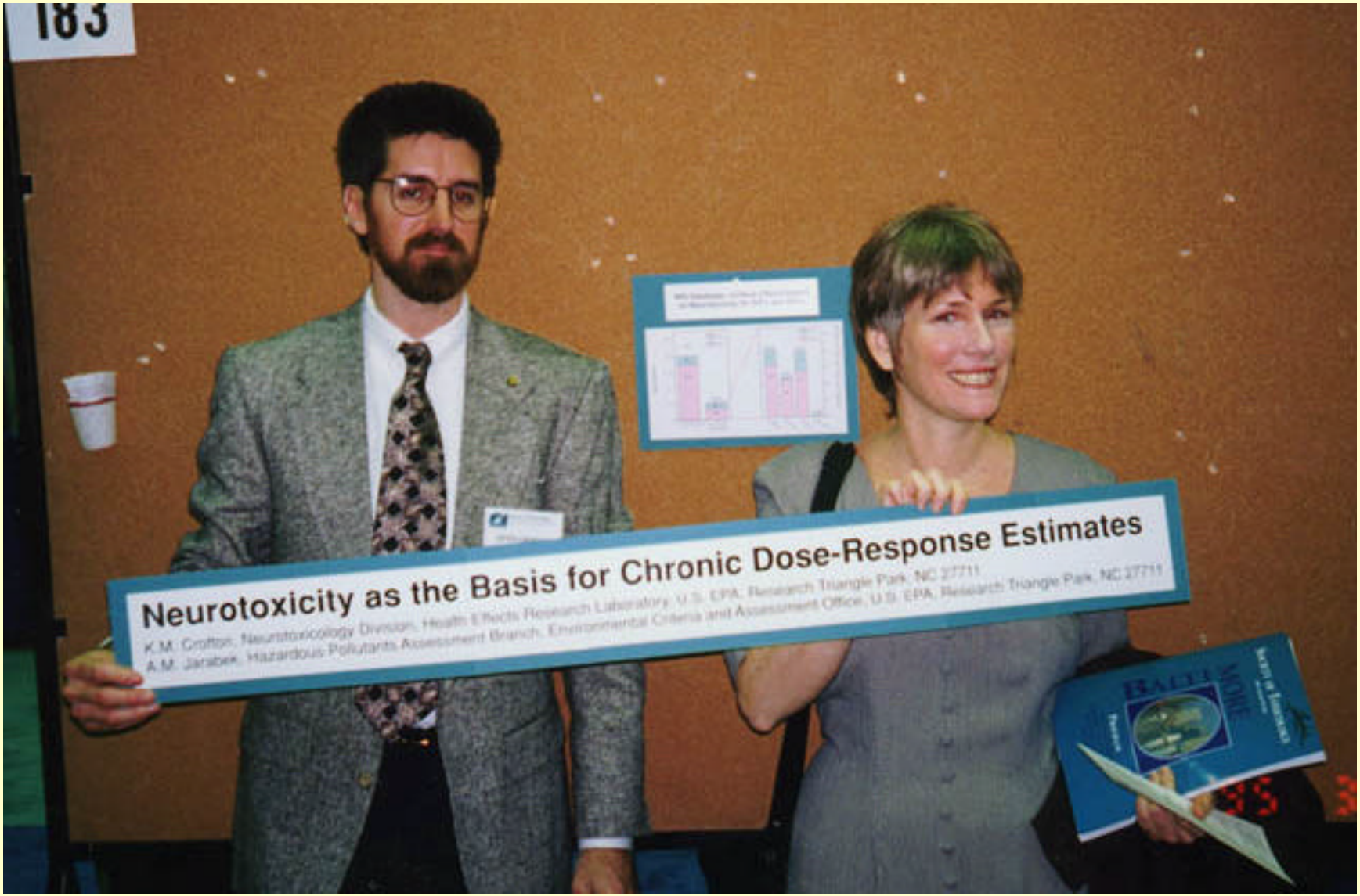
Mechanisms of Thyroid Toxicity

Kevin M. Crofton

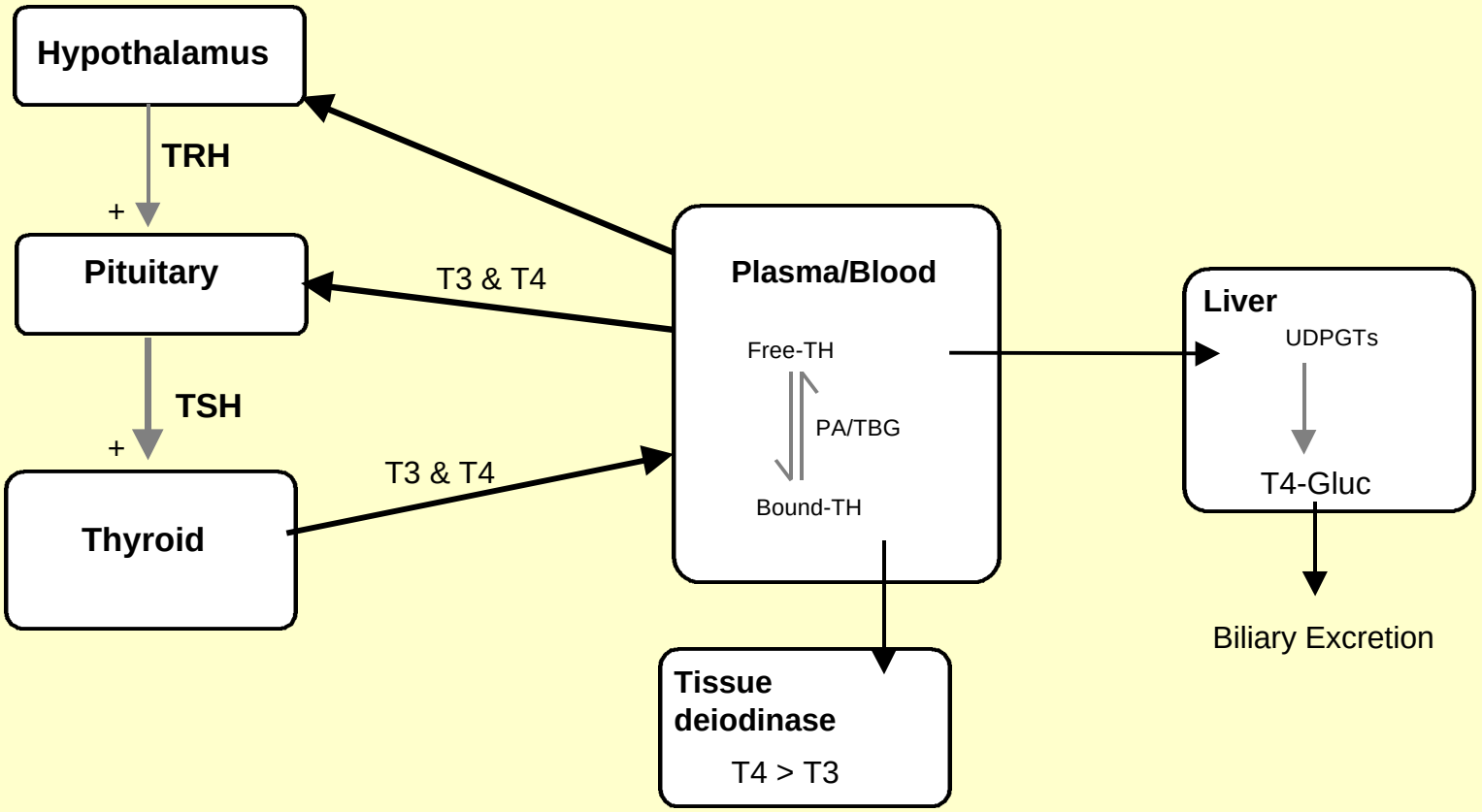
Neurotoxicology Division
National Health and Environmental Effects Laboratory
US Environmental Protection Agency
Research Triangle Park NC


183
Neurotoxicity as the Basis for Chronic Dose-Response Estimates
K.M. Crofton, Neurotoxicology Division, Health Effects Research Laboratory, U.S. EPA, Research Triangle Park, NC 27711
A.M. Jarabek, Hazardous Pollutants Assessment Branch, Environmental Criteria and Assessment Office, U.S. EPA, Research Triangle Park, NC 27711

Outline

1. Introduction to thyroid hormones
2. Effects of perchlorate
3. Effects of the disruption of thyroid hormones
    - Thyroid hyperplasia and neoplasia
    - Developmental abnormalities
4. Uncertainties

Hypothalamus-Pituitary-Thyroid-Liver Axis



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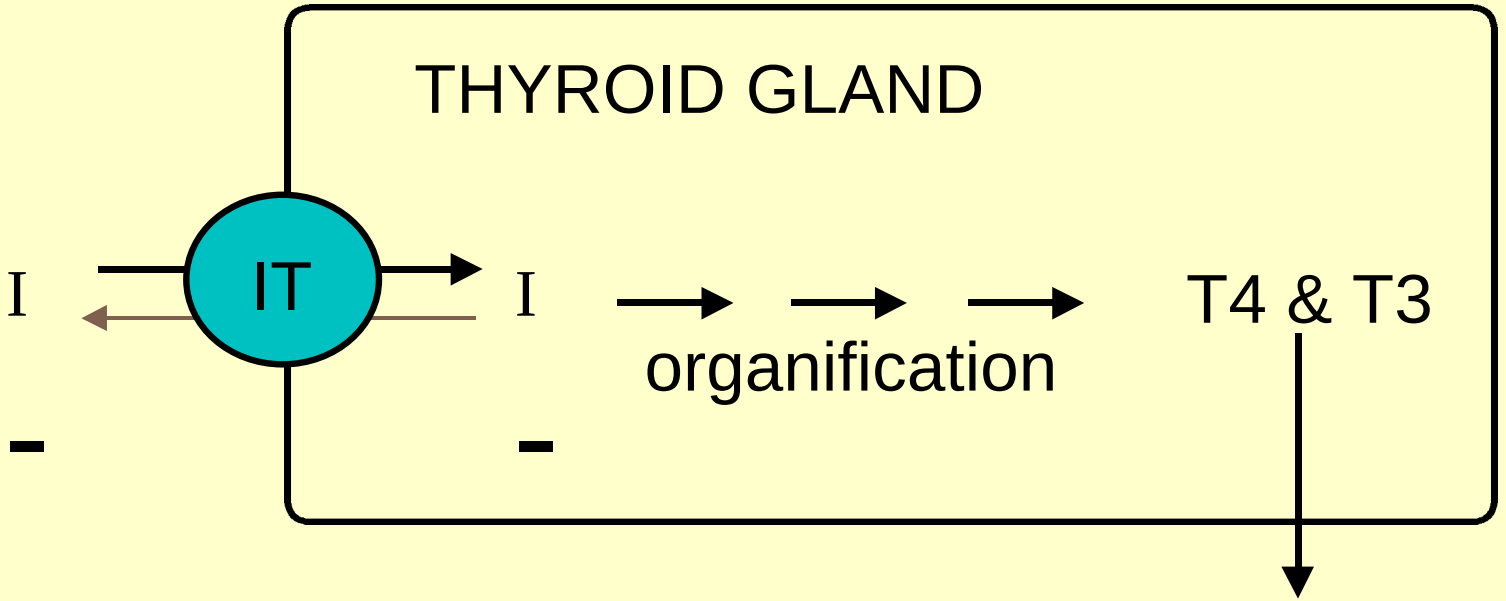
Iodine and the Thyroid Gland



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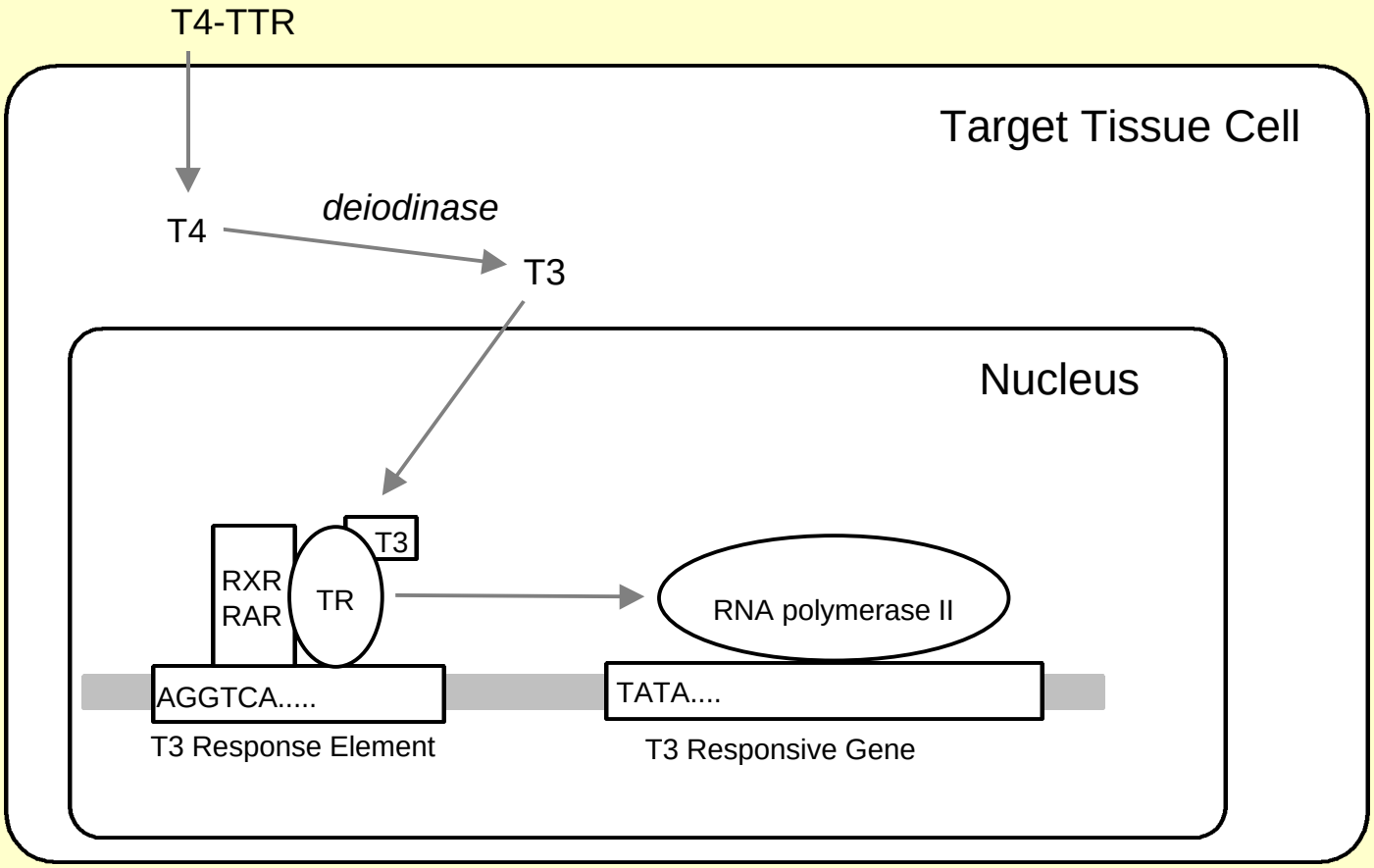
Thyroid Hormone Receptors and Thyroid Response Elements



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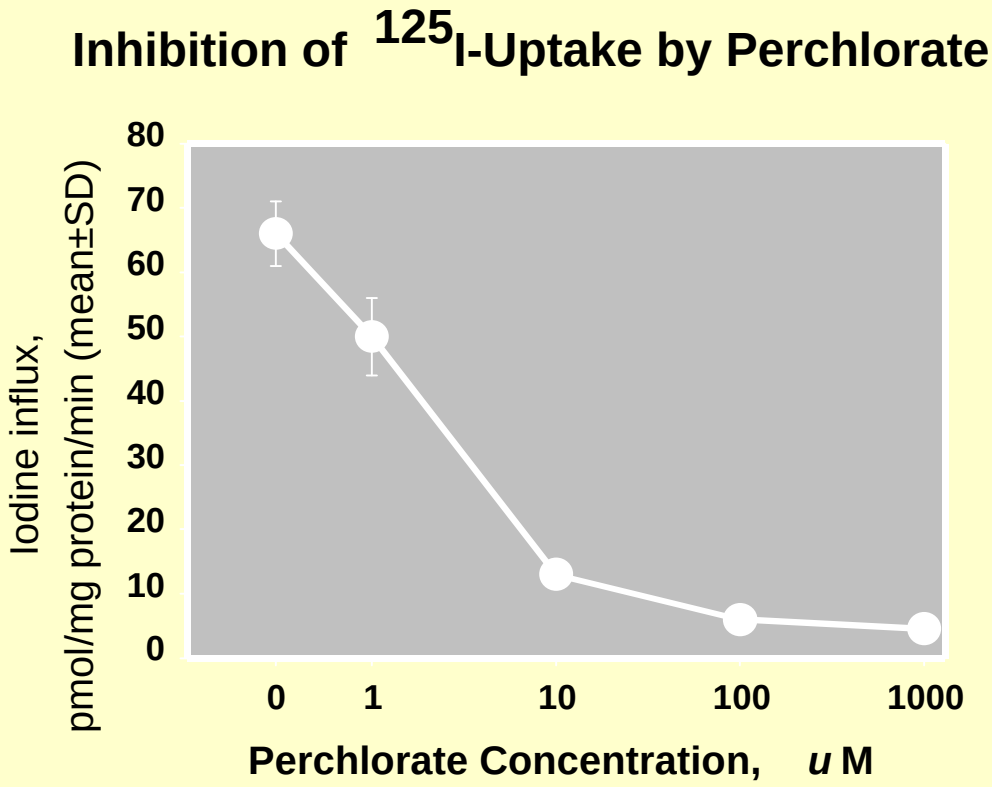
Targets for Environmental Chemicals

- **Thyroid Gland**
  - ➡**uptake process**
  - ➡**organification**
  - ➡**release**
- **Plasma Transport Proteins**
- **Tissue Deiodinases**
- **Hepatic Glucuronidation and Sulfation**

In Vitro Thyrotoxicity of Perchlorate



(Gerard et al., 1994)

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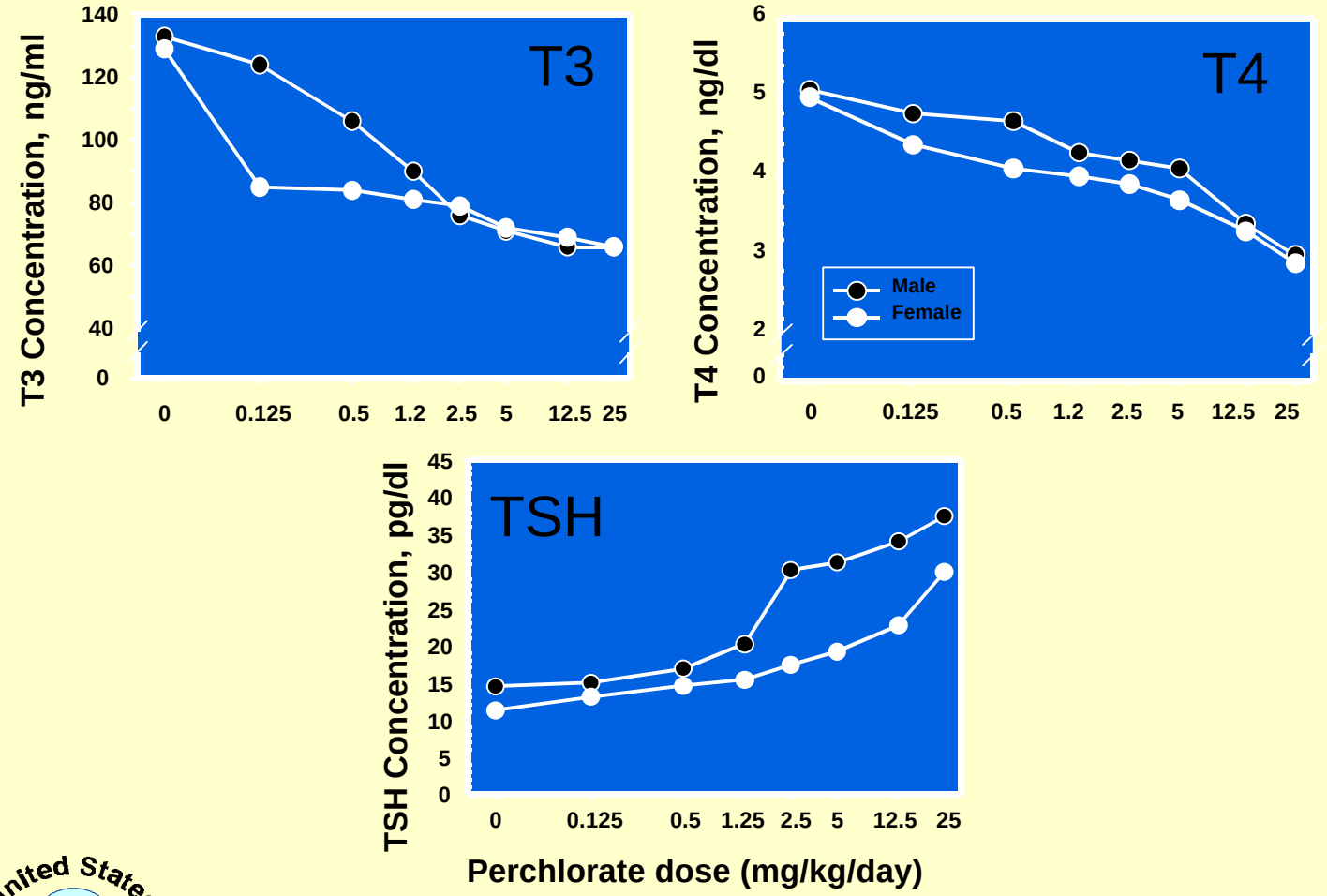
14-Day In Vivo Perchlorate Study



(Caldwell et al., 1994)

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Effect of TH disruption

- **Adult**
  - **Main effect of prolonged depression of TH is upregulation of TSH which leads to thyroid gland hyperplasia**
- **Developmental**
  - **Main effect is the disruption of developmental processes**

Main Symptoms/Effects of Hypothyrodism

Developmental

- delayed reflex ontogeny
- impaired fine motor skills
- deaf-mutism, spasticity
- gait disturbances
- mental retardation
- speech impairments

transient disruption leads to permanent effects

Adult

- run down, slow, depressed,
- sluggish, cold, tired
- dryness and brittleness of hair
- dry and itchy skin, constipation
- muscle cramps
- increased menstrual flow

transient disruption leads to transient effects

*thyroid tumors in rodents

Data Deficiencies

- **Long-term periodic exposures**
  - **Perchlorate kinetics**
  - **Thyroid hormone homeostasis**

- **Effects during development**

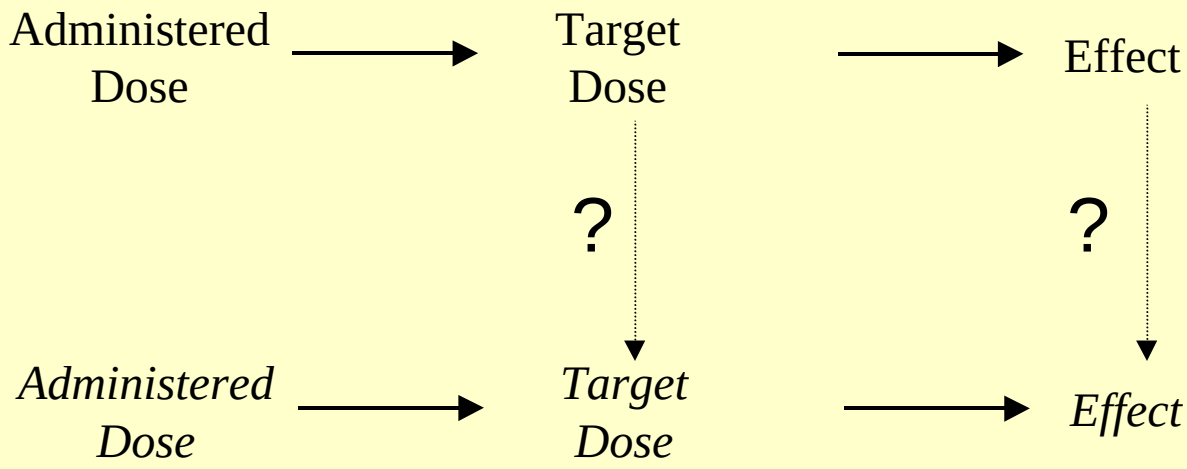
Uncertainties in Risk

1. Animal to Human Extrapolation

2. Age-Dependent Sensitivity

Uncertainties Due to Potential Species Differences

Rat



Human

ADME studies

Mechanistic / Sensitivity Studies
1. Adult
2. Developmental

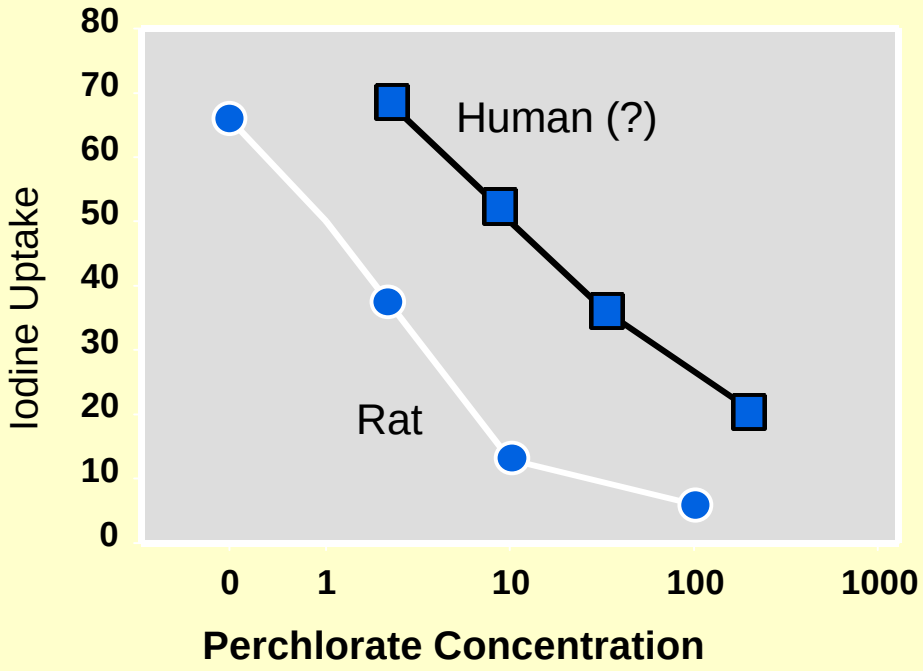
Mechanistic Studies

- Aid to quantitative interspecies extrapolation - basis to extend PBPK model
- Additional developmental studies to evaluate thyroid TH in fetal and post-natal periods
- Determine relative sensitivity of fetal/postnatal thyroid versus adult
- Determine relative sensitivity of rat versus human

Resolving Uncertainties
Mechanistic Studies

Do species differences exist?

compare rodent and human sensitivities using in vitro techniques



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Uncertainties in Risk

2. Age-Dependent Sensitivity
   - Developmental effects can be permanent.
   - Is the developing organism more sensitive?

Yes - need to carefully characterize

No - protection of maternal compartment

ADME study

- Literature review of perchlorate discharge test
- Protocols proposed to evaluate perchlorate kinetics, iodine inhibition kinetics and thyroid hormone homeostasis
- Basis for development of physiologically-based pharmacokinetic (PBPK) model

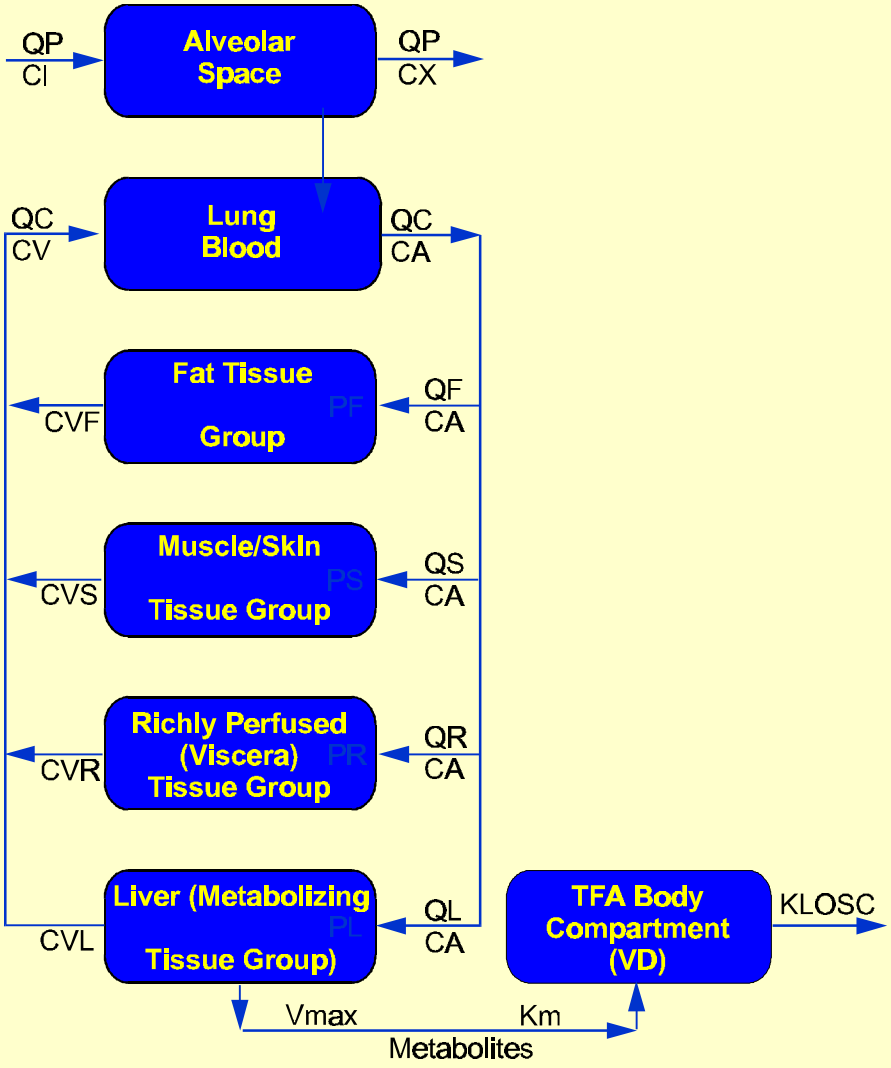
Resolving Uncertainty - Example

2. Age-Dependent Sensitivity

Determine relative sensitivity of fetal/postnatal thyroid versus adult

Determine relative sensitivity of rat versus human

PBPK Model Schematic



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Summary

- Facts:
  - Perchlorate cause hypothyroidism
- Uncertainties
  - Animal to Human extrapolation
  - Age-dependent senstivity